

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of:

Juha-Matti SAVOLA et al.

Serial Number: 10/534,091

Group Art Unit: 1618

Filing Date: May 6, 2005

Examiner: Gembah, Shirley V.

For: OROMUCOSAL FORMULATION AND PROCESS FOR PREPARING THE SAME

DECLARATION PURSUANT TO 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Christian Funck-Brentano, MD, PhD, hereby declare as follows:

1. I earned my MD from Pitié-Salpêtrière University in 1982, and completed my internal medicine and cardiology training within the hospitals of Assistance Publique-Hôpitaux de Paris. I trained in clinical pharmacology at Vanderbilt University, Nashville, Tennessee from 1986 to 1988, and received my PhD in Clinical Pharmacology at Paris 6 University in 1990.

2. I am Director of the Clinical Investigation Center at St. Antoine University Hospital, Paris, France, and a Professor of Medicine and Clinical Pharmacology at Pierre et Marie Curie University Medical Center.

3. I have authored over 120 scientific papers concerning drug metabolism, drug-drug interactions, drug-induced QT interval prolongation, cardiac arrhythmias and cardiovascular clinical trials.



4. I am a member of the Committee for Practice Guidelines from the European Society of Cardiology since 2006, a member of the French Society of Cardiology and of the French Society of Pharmacology and Therapeutics. I am past president of the Association of Pharmacology Teachers of French Medical Schools. I served on the Editorial Board of the Journal of Cardiovascular Pharmacology from 1993 to 1998.

5. My curriculum vitae is attached.

6. I am not one of the inventors of the invention described and claimed in U.S. Patent Application Serial No. 10/534,091 ("the application"). I am also not an employee of the owner of the application, Santhera Pharmaceuticals (Switzerland) Ltd., or any of its related companies or predecessors-in-interest.

7. I have read and understand the application, including pending claims 23 and 25-33. I have also read and understand the references cited against these claims in the Official Action dated August 2, 2010 ("the Official Action").

8. The Patent Office examiner has cited Funck-Brentano et al., "Rate Dependence of Sotalol-Induced Prolongation of Ventricular Repolarization During Exercise in Humans," 83 Circulation 536 (1991) (hereinafter "Funck-Brentano") to support her argument that QTc prolongation or its absence can be predicted from heart rate. See page 4, lines 12-20 of the Official Action.

9. I am the lead author of Funck-Brentano. My article does not support the examiner's argument. Moreover, her argument that QTc prolongation or its absence can be predicted from heart rate is incorrect, as explained in detail below.

10. QT interval is the electrocardiographic parameter which represents the duration of depolarization and repolarization in the heart. It is well known that QT interval is influenced by heart rate (Bazett HC. An analysis of the time-relations of electrocardiograms. Heart. 1920;70:353-70; Fridericia LS. Die Systolendauer im Elektrokardiogramm bei normalen Menschen und bei Herzkranken. Acta Med Scand 1920; 53:522-34). It shortens when heart rate increases and prolongs when heart rate decreases.

11. In order to assess the influence of external factors, such as disease states or drugs, on ventricular repolarization one has to consider the QT interval corrected for heart rate, the QTc. QTc represents the duration of QT normalized to a heart rate of 60 bpm (i.e. an RR interval of 1 sec). The correction process uses an empirical formula which reflects the relationship between uncorrected QT intervals and RR intervals at which QT is measured. However no standard formula exists and several methods of QT correction have been proposed (Funck-Brentano C, Jaillon P. Rate-corrected QT interval: techniques and limitations. Am J Cardiol. 1993;72:17B-22B). All these methods are questionable because the



correction they yield is not always perfect, i.e., QTc is not always truly independent from heart rate.

12. The purpose of QT interval correction, therefore, is to take into account the influence of heart rate on uncorrected QT interval and express QT independently from heart rate, hence the QTc. When, QT correction is made appropriately, it yields a QTc which, by definition, should be independent from heart rate. If it is not, this indicates that the correction formula which is used is improper. The quality control of a good QT correction is to plot QTc as a function of heart rate (or RR interval) and show that the slope of this relationship is zero.

13. In conclusion QTc prolongation cannot be predicted from heart rate or at least should not if the correction process is appropriate. By definition, if the correction is performed appropriately, QTc interval is independent from heart rate.

14. Funck-Brentano examines the rate-dependence of uncorrected QT prolongation with sotalol. This so-called inverse-rate dependence, in contrast to the effects of sodium channel blockade on QRS interval duration, means that the effect of a QT prolonging drug, such as an IKr blocker, on repolarization increases when heart rate decreases. We assessed sotalol-induced QT-prolongation over a wide range of heart rates. Our study showed that, in the case of the IKr blocker sotalol, QT interval prolongation was more pronounced at slow than at fast heart rates.

15. Funck-Brentano also discusses the best QT correction method using raw QT-RR data. In order to avoid the errors of using the standard Bazett's QT correction formula (which, as discussed above, is empirical and potentially biased), we used several fitting functions and choose the one which had the best fit and therefore was less biased. This allowed the analysis of QT changes without sotalol and during administration of 3 dosages of sotalol at various heart rates.

16. The relationship between corrected QT (QTc) and heart rate was not specifically studied in this study, i.e. we did not plot QTc obtained from raw QT-RR intervals measured at various heart rates as a function of heart rate. The reported QTc interval merely represents the best fitted QT interval at a heart rate of 60 bpm (RR interval of 1 sec.), the QT_{1000 msec}. This QTc value was not the result of the correction of a QT interval measured at a heart rate very distant from 60 bpm but the best mean value of the QT measurements truly performed at a heart rate of or close to 60 bpm.

17. Of note, the correction formula we used in Funck-Brentano was recently showed to be appropriate to correct heart rate in guinea pig heart preparations exposed to a QT-prolonging drug (Tabo M, Komatsu R, Isobe T, Honda M, Yamada Y, Kimura K. Accurate detection of drug-induced delayed ventricular repolarization with a suitable correction formula in Langendorff guinea pig heart. J Toxicol Sci 2010; 35:687-98).

18. All statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent resulting therefrom.

Signed this 3rd day of November, 2010.



Signed: _____
Dr. Christian Funck-Brentano

Exhibit:
Curriculum vitae of Dr. Christian Funck-Brentano



Curriculum Vitae - Pr Christian FUNCK-BRENTANO

Department of Pharmacology and Clinical Investigation Center

Pierre & Marie Curie University - School of Medicine

Department of Pharmacology - Pitié-Salpêtrière University Hospital

75651 - Paris Cedex 13 - FRANCE

e-mail: christian.funck-brentano@upmc.fr

Christian FUNCK-BRENTANO M.D., Ph.D. Born in 1955

Married, 2 children (1980 et 1983).

Nationality: French

Bilingual English / French.

CURRENT POSITION:

- Professor of Clinical Pharmacology - Hospital Practicing Physician. Department of Pharmacology, Pitié University Hospital, Paris. Head of Department
- Director of the Clinical Investigation Center, CIC Paris-Est, Pitié-Salpêtrière University Hospital, Paris since 2005 (Associate Director from 1993 to 2004).

UNIVERSITY STUDIES AND DIPLOMAS:

- Medical Degree (unrestricted licence to practice general Medicine in France): Paris 6 University, 1982.
- Board Certification in Cardiology (unrestricted licence to practice Cardiology in France): Paris, 1986.
- Board Qualification in Internal Medicine: Paris, 1994.
- Paris University Hospitals' Residency (numerous clauses examination with 10 % passing rate, offering 4 years (8 x 6 months) of training in Paris University Hospitals: 1979-1981 (Geriatrics, Cardiology, Internal Medicine, Cardiology) and 1983-1985 (Intensive Care Unit, Cardiology, Hypertension, Arrhythmia Unit).
- Silver Medal of Paris University Hospitals' Residency (one additional year of training - Arrhythmia Unit): 1985-1986.
- Head of Clinics - Assistant: (Clinical Pharmacology Unit, St-Antoine University Hospital): 1988-1990
- Assistant Professor of Clinical Pharmacology (St-Antoine): 1990-1992.
- Associate Professor of Clinical Pharmacology (St-Antoine): 1992-1996.
- Professor of Clinical Pharmacology since 1998.
- Master in Human Biology (General Pharmacology): 1980-1982.
- Diploma of Extended Research in Human Biology (2 years of training at the Hepatic Pathophysiology Research Unit, INSERM U24 - studies of hepatic drug metabolism): 1981-1983.
- Educational Commission for Foreign Medical Graduates: 1984.
- University Diploma of Clinical Pharmacology (St-Antoine): 1988.
- Ph.D. Thesis (Pharmacology, Paris 6 University): Pharmacogenetics and enantiomers of antiarrhythmic drugs, 1990.
- Director of Research Diploma (highest degree awarded by a French University): Paris 6 University, Paris, 1991.

RESEARCH TRAINING:

- 1981-1983: 2-year basic research training at the Hepatic Pathophysiology Research Unit, INSERM U24, Pr JP Benhamou.
- 1985-1986: 1-year clinical research training at the Arrhythmia Unit, Lariboisière University Hospital, Pr Ph Coumel.
- 1988-1989: 2-year training at the General Clinical Research Center - Division of Cardiology and Division of Clinical Pharmacology, Vanderbilt University, Nashville, TN, USA, Raymond L. Woosley and Dan M. Roden. Clinical Pharmacology Studies (phase I to III) in the field of cardiovascular drugs and pharmacogenetics. Basic electrophysiological studies in multicellular animal models.

PUBLICATIONS: PubMed link H-index : 39

- > 140 original articles in international peer-reviewed journals.
- 19 general reviews (including 1 in *N Engl J Med*) in international peer-reviewed journals.
- 11 book chapters.
- Editorial Activities:
 - Member of the Editorial Board of *J Cardiovasc Pharmacol*: 1993 - 1998.
 - Member of the Editorial Board of *Fundam Clin Pharmacol*: 1991-2002
 - Reviewer of more than 200 original articles (4/5 being sent by peer-reviewed international journals) since 1988.

GENERAL INTEREST ACTIVITIES AND EVALUATIONS:

- Member of the Committee for Practice Guidelines from the European Society of Cardiology: since Sept. 2006
- Member of the Scientific Advisory Committee of QT Drugs (<http://qls.univ-paris5.fr/>)
- Member of the Expert Scientific Commission of the Assistance Publique - Hôpitaux de Paris: 2004-2009
- Member Scientific Council of "LEEM Recherche" 2008-2010
- Member of the Scientific Development Council of the AGEPS (General Agency of Equipments and Health Products) - Paris: 2008-2010
- Member of the Scientific Council of AFRETH since 2009
- Member of the Council for Clinical Investigation and Evaluation of Diagnostic and Therapeutic Procedures at the INSERM: 1991-1995.
- Correspondent to the Clinical Research Delegation at the Assistance Publique - Hôpitaux de Paris (AP-HP): 1991-1995.
- Member of the Expert group for the Scientific and Technical Mission of the Ministry of Universities and Research (DSPT 5): 1994-1996.
- Member of the Scientific Committee at the Clinical Investigation Center (C.I.C.) at St-Antoine University Hospital: since 1994.
- Reviews of protocols for the CPHS of Paris - Pitié-Salpêtrière.
- Collaborations with the French Medicine Agency (E.C. guidelines).
- Participation to the conception of the National Program of Clinical Investigation Centers (with the Ministry of Research and the INSERM).
- Member of the Clinical Investigation Committee at the INSERM: 1999-2003.
- President of the Association of Pharmacology Teachers of French Medical Schools: 2000-2007.
- Member of the French College of Medical Pharmacologists (Council member)

SCIENTIFIC SOCIETIES:

- Fellow of the European Society of Cardiology (FESC)
- Member of the French Society of Pharmacology and Therapeutics.
- Member of French Cardiology Society. Arrhythmia group.
- Member of the "Groupe de Réflexion sur la Recherche Cardiovasculaire": 1990-2000.

AWARDS AND DISTINCTIONS:

- Award from the Committee for Scientific and Technical Research, Ministry of Research Bourse DGRST and from the Claude Bernard Association, 1981 and 1982.
- Silver Medal of Paris University Hospitals' Residency, 1985.
- Merck Sharp & Dohme International Fellowship in Clinical Pharmacology (2 years in the USA), 1986.
- Award from the "Fond d'Études du Corps Médical des Hôpitaux de Paris", 1989 and 1990.
- Paul Neuman Price in Clinical Pharmacology, 1990.
- 6 Clinical Research Contracts from the AP-HP, 1982, 1990, 1991, 1993, 2001.
- External Research Contract, INSERM, 1981-1984.

OTHER ACTIVITIES:

- Director Master of Clinical and Experimental Pharmacology, UPMC, Paris. Teaching to Medical Students in Pharmacology, Cardiology, Therapeutics, UPMC - School of Medicine. Masters of Cardiovascular and Respiratory Pharmacology, Methods in Clinical Trials. National coordinator of the Web project for Pharmacology Students in French Medical Schools (2000-7).
- Member of several Critical Events / Endpoint Committees of large scale multicenter clinical trials (AMIBIS - CIBIS 1, 2 and 3 - INSIGHT - PRINCESS - MOTIV) and of several DSMBs.
- Chairman of the Critical Events Committee of CIBIS 2 (2560 pts included in an European mortality trial in heart failure patients. Head of the Medical Coordinating Center of this trial, 1995-1998. Chairman of the Endpoint Committee of CIBIS 3.

RESEARCH INTERESTS: (key words)

- Antiarrhythmic drugs and effects (QT prolongation), electrocardiography, electrocardiogram pattern, cardiac adverse events, drug interactions, hepatic drug metabolism *in vivo*, pharmacogenetics, cytochromes P-450, CYP2D6, CYP2C19, drug transporters, Individualized Drug response, Personalized Medicine.
- Cardiovascular drugs, Phase I and II studies, QT interval.
- Phase III : Critical Events (Endpoint) Validation, Cardiac Safety, Medical Coordination.

Christian Funck-Brentano

03 November 2010